HAIR TRANSPLANT forum INTERNATIONAL

INTERNATIONAL SOCIETY OF HAIR RESTORATION SURGERY

Volume 18, Number 3
May/June 2008

COLUMNS

FEATURE ARTICLES

Do we need hair follicle stem cells and hair follicle neogenesis to cure common hair loss disorders?

Ralf Paus, MD *Lübeck, Germany & Manchester, United Kingdom*

Few concepts have ingrained themselves as quickly with physicians who treat hair loss as the vague notion that to cure the common causes of alopecia and effluvium, somehow, one needs to be able to manipulate hair follicle stem cells, either by forcing them to "behave" in a manner that clinically and cosmetically desired hair growth results are obtained, or by injecting them so as to induce the formation of new hair follicles. It has attained almost the status of conventional wisdom that injecting just the right kind of stem cells will usher in a brave new age of iatrogenic hair follicle neogenesis, where newly created hair follicles (either generated directly in adult skin or even *in vitro* from autologous cells, which are then re-transplanted), at long last, will produce the youthful, fully pigmented terminal scalp hairs that had fallen victim, for example, to the baldness-promoting activities of androgens.

Based on these beliefs, on the one hand, biotech companies with a focus on hair follicle neogenesis or stem cell–based hair loss therapy have been founded. On the other hand, hair transplant surgeons increasingly worry that their time-honored and effective surgical procedures for predictable hair restoration will soon become outdated, with hair transplant surgery slowly sliding down a relentless path towards ultimate extinction. The lay public, in turn, especially if aggrieved by a personal hair loss problem, and encouraged in this perception by mass media infatuation with anything that rings of stem cells and organ regeneration, is getting increasingly impatient with us physicians: "Why does it take you guys so long to just make new hair follicles pop up in the balding plate…?!"

"Hair follicle–associated stem cells undoubtedly hold a lot in store for regenerative medicine—well beyond skin and the hair follicle—but they are not going to put hair transplant surgeons predictably out of business any time soon."

Yes, the pressure is on. Just the right time to lean back and to reflect, calmly and carefully: What are these much-reverberated views really based on? Do we actually need hair follicle stem cells and/or hair follicle neogenesis to successfully treat (or even cure) common hair diseases? Will hair restoration surgery really become replaceable in the foreseeable future?

In the following lines, I shall develop some personal, quite possibly controversial and provocative, arguments in response to these pertinent questions (for more background and some relevant references see, for example, Paus, R., *Drug Discov Today* 2006). The underlying views are those of a clinical dermatologist with roughly two decades of experience both in basic hair research and in treating patients with hair growth disorders.

Basic Facts of Hair Loss

For starters, let us recall a few simple facts about hair loss that must serve as the cornerstone for the discussion at hand:

1. By far, the far most common hair loss disorders in daily practice as well as in specialized alopecia clinics are androgenetic alopecia (of the male or female pattern variant), various causes of effluvium (the majority of which may represent telogen effluvium associated with androgenetic alopecia and/or thyroid abnormalities), and alopecia areata.

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Hair Transplant Forum International
Volume 18, Number 3

Hair Transplant Forum International is published bi-monthly by the International Society of Hair Restoration Surgery, 13 South 2nd Street, Geneva, IL 60134. First class postage paid at Chicago, IL and additional mailing offices. POSTMASTER: Send address changes to *Hair Transplant Forum International,* International Society of Hair Restoration Surgery, 13 South 2nd Street, Geneva, IL 60134. Telephone: 630-262-5399, U.S. Domestic Toll Free: 800-444-2737; Fax: 630-262-1520.

President's Message

Bessam K. Farjo, MD *Manchester, England*

While it may not be absolutely necessary to attend every ISHRS Annual Scientific Meeting, there has never been one where I did not feel I learned a valuable technique, heard a word of wisdom, or picked up a valuable pearl. This could have happened at a lecture, workshop, outside in the corridor, or even over a drink or dinner. The networking value of the meeting is worth the registration fee alone. For beginners or colleagues early in their careers, the meeting must be a real eye-opener. Top all this with the chance to meet again with old friends or make new ones, and you come to realise why we go every year.

Increasingly I come across fellow physicians (independent or via their employing clinics) who boast of their pride at being "active" ISHRS members in their literature or promotions. Some tell of their scientific and research "contributions" to the Society. Some tell of their inventions, exclusive techniques and equipment, expert status, and so-called leadership. Yet when you look at the ISHRS website, you find they have been to very few meetings or none at all! They recognise the status of the ISHRS yet they don't come. They claim expertise and know-how yet they don't demonstrate it or share it at ISHRS meetings. Why is that?

Well, maybe it is much easier to make such claims to the lay patient who does not normally ask for scientific scrutiny. As great as the Internet has been in spreading the good word about today's fantastic transplant results, it has unfortunately also provided a breeding ground for self-styled "experts and leaders." As a result, we all now get email enquiries along the lines of "How much do you charge for x thousands of grafts?" or "Do you do hair multiplication?" or "Do you do scarless surgery?" In certain countries, there is some policing about what can and cannot be said in an advert, but not so on the Internet. Some of the physicians I am referring to seem to produce very good work, but market themselves by creating the mystique of "I know a secret way no one else knows about." Alternatively, it could be that they actually fear scrutiny by their colleagues were they to present their case at a meeting.

We are always learning no matter how advanced our level as this is how we best serve our patients. Worldwide our field is at the level of achievement it is now because of the vision of leaders and their recognition of the need to share knowledge and willingly teach those who seek it. This was one of the reasons why the ISHRS was actually founded. Sharing a concept or technique that has merit and is of benefit to patients is certainly an ethical requirement of every medical practitioner.

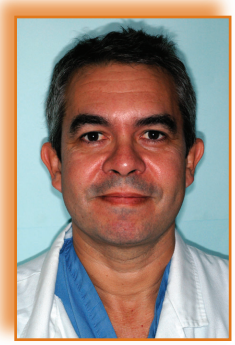
I have just come back from the Orlando Live Surgery Workshop and nowhere can you see the above principles demonstrated more. The workshop was sponsored by the ISHRS and this year in particular there appeared to be a very high number of newcomers to the field. At the surgery centre especially, the selfless tuition and demonstration was remarkable. For the beginners, it was like kids in a sweet shop! Hats off once again to Drs. Matt Leavitt, David Perez-Meza, Marco Barusco, and the rest of the team of physicians and technicians. A huge thank-you as well to the fantastic faculty for giving their time so generously.

Because of all this I encourage everyone with a genuine interest in this field of ours to attend as many of our annual scientific meetings as possible and contribute to the knowledge of all of us by sharing your pearls and experiences and discussing your ideas and techniques. Make a start or continue to share and contribute at the meeting in Montréal in September.

Bessam Farjo, MD

Co-editors' Messages

Paco Jimenez, MD *Las Palmas, Spain*



In this issue of the *Forum* we have received a variety of very interesting articles, ranging from clinical studies and surgical techniques to technological innovations. In the field of new technologies, Miguel Canales, Medical Director of the company Restoration Robotics, explains the potential benefits of robotics in hair transplantation. They are currently evaluating a robot capable of harvesting follicular units. According to Canales, as this robotic prototype "is developed and optimized, it may be possible to achieve harvest speeds of up to 1,000 follicular units per hour." I am sure you will agree how much of a help that would be to all of us!

Jeff Teumer, Research Director at Intercytex, summarizes the different strategies in relation to hair cloning, namely the production of thousands of follicular cells with regenerative properties that can be introduced later in the patient's scalp to induce the formation of hair—another topic that we as hair transplant surgeons follow with great interest.

Another innovation that will give much food for thought is the appearance on the Internet market of a screening test for AGA. Dr. Sharon Keene explains the scientific fundaments of this test. Its main advantage, according to Dr. Keene, would be "to identify a high-risk population of AGA, prior to visible signs of hair loss, for the purpose of early medical intervention."

From a surgical standpoint, we have two articles in this issue. The Brazilian hair transplant surgeon Dr. Fernando Basto shows us in detail how he positions the patient (in dorsal decubitus) during the procedure, allowing Dr. Basto's team to perform the donor closure, follicular unit dissection, and hair graft placement at the same time. Dr. Nagai, from Japan, writes on the difficulties encountered when harvesting graft from non-scalp areas, such as the thigh. Differences in elasticity of the skin and the acute angles of exiting the hair in the skin are among other factors that Dr. Nagai emphasizes as the cause of the high transection rate.

With respect to clinical studies, Dr. Bernard Cohen explains how hair breakage is the factor responsible for hair loss in a significant number of long-haired women. Hair breakage may be unnoticed by visual inspection, but can be easily detected and quantified using the trichometer, a device developed by Dr. Cohen that measures the quantity of hair in a particular area of the scalp. I envision this device becoming a great advance as a non-invasive method for quantifying hair loss and hair growth.

We feel particularly thankful to Dr. Stough for writing an update on the side effects of finasteride. Given Dr. Stough's extensive experience with clinical trials in the use of finasteride and dutasteride, all his comments are full of authority.

Finally, it is a great honor for our journal to receive a paper from one of the most prominent researchers in hair biology, Dr. Ralf Paus from Germany. He is an authentic leader, a prolific writer, and an outstanding speaker. Personally, I have always enjoyed his lectures and I envy his ability to suggest thought-provoking ideas. I am sure you will savor and enjoy what Dr. Paus has prepared for us.

Paco Jimenez, MD

Bernard Nusbaum, MD *Coral Gables, Florida*

One of the vital functions of the *Forum* is to provide the latest information on new and emerging technology in our field—not only for the purpose of assessing the impact of new treatments on patient management, but also to inform the membership of factors that may affect their practice in the future. This information will help to provide up-to-date answers to the questions that arise daily in this age of the Internet-educated patient. This issue engages distinguished authorities in their particular fields to provide updates and opinions on novel and controversial areas of hair restoration surgery.

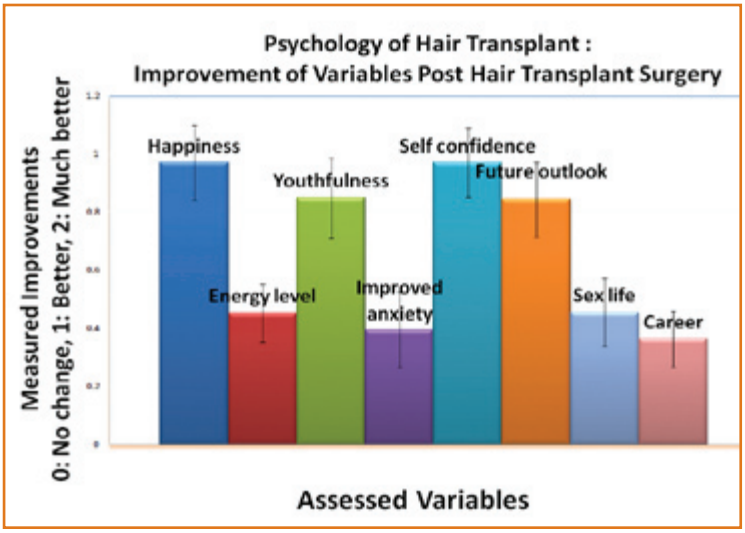
We are also proud to announce a stellar achievement for our Society. The ISHRS recently received certification of "Exemplary Performance" and "Accreditation with Commendation" from the Accreditation Council for Continuing Medical Education (CME), which is the utmost level of accreditation any educational provider can receive from the most respected medical education credentialing body in the United States. The editors would like to congratulate Drs. Paul Cotterill and Bob Haber along with Victoria Ceh and Kimberly Miller as well as the entire ISHRS CME Committee for this outstanding accomplishment. We also congratulate all of you who participate in our meetings and programs for helping to produce high-quality educational events that are such a positive reflection on the field of hair restoration as a whole. For some of our international members who may not be familiar with the CME concept, continuing medical education has the purpose of educating physicians to maintain competence and incorporate new knowledge to improve patient outcomes. In the United States, most state governments and hospitals have CME requirements that must be met for physicians to maintain their licensure and/or hospital privileges.

In this regard I would like to encourage all of you to qualify and obtain the ISHRS CME Award. Its purpose is to recognize physicians who have earned a specified number of CME credits, and notation of the award is included by the physician's name in the ISHRS website "Find a Doctor" database. The application for the award can be obtained on the Society's website in the "Members Only" section; as more of us achieve this certification, the more credibility that it will attain.

Educational credentials seem more relevant at a time when there appears to be a tendency in some countries around the world for governmental regulators to decide who should be allowed to perform hair restoration surgery. There are many opinions on the legitimacy or fairness of any such credentialing and regulation and, without question, developing criteria will be an extremely consequential and complex matter. Nevertheless, with the ISHRS, our field has an educational society in place with top level accreditation and fellowship training programs. We also have the ABHRS and IBHRS certification exam. Certainly, there is no perfect solution, and no educational program or examination can ensure competence, only a knowledge base. This is an extremely sensitive matter, and it seems prudent that the ISHRS would monitor such international developments, support the right of physicians to perform hair restoration surgery, and stress the importance of proper education.

Bernard Nusbaum, MD

Sorry...



My sincerest apologies to Drs. Parsa Mohebi and William Rassman for the illegible reproduction of their table "Psychology of Hair Transplant: Improvement of Variables Post Hair Transplant Surgery," which graced the cover of our March/April 2008 issue. While we try hard to ensure that these issues are caught prior to printing, this one slipped through.

The chart on the left has been updated on the electronic version of the issue, and can be found on the ISHRS website at www.ishrs.org.

Cheryl Duckler
Managing Editor, ISHRS *Forum*

ISHRS Welcomes Liz Rice-Conboy, Membership Manager

The ISHRS welcomes Liz Rice-Conboy as our new ISHRS Membership Manager. While we are sad to see Amy Whittaker, ISHRS administrative assistant, leave the ISHRS, we wish her the best on her decision to move on with her career. At the same time, we are pleased to welcome Liz Rice-Conboy to the ISHRS Administration Team. Liz comes to the ISHRS with her most recent experience working in board and committee relations, and independent project and task force management with the American Society for Surgery of the Hand. Aside from medical society management experience, Liz has also worked in the social service non-profit and training fields, and has a Masters in Applied Child and Family Studies. Liz is excited to expand her skills with the ISHRS in a position that has a little bit of everything, including answering the phones here at headquarters, and looks forward to meeting you in Montréal! Ask to see the most recent photo of her daughter, who is her pride and joy.

Guidelines for Submitting an Article to the *Forum*

- ✓ Send submission AND Author Consent Release Form electronically via e-mail to Bernie Nusbaum, MD, at drnusbaum@yahoo.com.
- ✓ Include all photos and figures referred to in your article as separate *attachments* in JPEG or TIFF format. Be sure to attach your files to your e-mail. Do *NOT* embed your files in the e-mail itself.
- ✓ An Author Consent Release Form must accompany your submission. The form can be obtained in the Members Only section of the website at www.ishrs.org.
- ✓ At the beginning of any article submitted for the *Forum*'s consideration, authors must disclose any financial or other commercial interest they possess in an instrument, pharmaceutical, cosmeceutical, or similar device referenced in, or otherwise potentially impacted by, the article.
- ✓ Trademarked names should not be used to refer to devices or techniques, when possible.

Submission deadlines:
June 5, July/August 2008
August 5, September/October 2008
October 5, November/December 2008

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Notes from the Editor Emeritus

Dow B. Stough, MD *Hot Springs, Arkansas*

5-alpha Reductase Inhibitors: More Questions, Fewer Concerns

It has been 10 years since finasteride was approved for use in North America by the FDA. Hair restoration surgeons have a wealth of experience with this drug and remain the leaders in disseminating information and educating others on their knowledge and proper use of this drug. Fortunately, our community does not have to strictly adhere to the prescribed label indications. For example, finasteride is indicated for men 18–41 years of age. These recommendations reflect the inclusion criteria of the protocols used to conduct clinical trials. All drugs must have age guidelines to conduct trials and finasteride is no different. As physicians, we commonly prescribe outside of these age guidelines. A distraught 17-year-old with male pattern hair loss could certainly be a candidate if all parties are agreeable, recognize the need for lifelong therapy, expense and possible side effects. Likewise, a 55-year-old male may be a wonderful candidate for 5 alpha-reductase therapy prescribed in conjunction with a hair restoration procedure. Perhaps the group of patients who receive the most benefit are those with combination therapies, for example, topical minoxidil plus a 5 alpha-reductase inhibitor (Figures 1 and 2). I have long felt patients with the largest hair caliber (> 80 microns) will obtain the best results with the current FDA proven medical therapies. It is taken for granted by most hair restoration surgeons that men with early onset male pattern baldness have the opportunity to experience the best results with 5 alpha-reductase inhibitors. Individuals who are fortunate to have large-caliber hair will be most likely to fall into the "greatly increased" results category. Those with fine-caliber hair will seldom make the poster-boy sessions in this category.

Figure 1. Dual medical therapy: 33-year-old Asian male after 8 months of finasteride and minoxidil foam. *Case history and photographs courtesy of Dr. James E. Vogel.*

Prostate Issues

My own confidence with this drug has increased over the years and I find myself prescribing finasteride to more and more patients. The rewards of 5 alpha-reductase therapy in male pattern baldness are readily apparent in our patients and published data. The benefit to the prostate gland are more subtle, though no less impressive. The Prostate Cancer Prevention Trial randomized over 18,000 men to treatment with finasteride or placebo. Only those with no prior diagnosis of prostate cancer and a low prostate-specific antigen were eligible. The evidence from an independent data and safety monitoring committee found that finasteride did substantially reduce the risk of prostate cancer. According to Dr. Ian M. Thompson of San Antonio, Texas, finasteride both reduces the risk of prostate cancer and improves the performance of screening tests for the disease. Finasteride accomplishes this by improving the sensitivity of the prostate-specific antigen test from 16.7% to 21.3%.

Figure 2. Dual medical therapy: 30-year-old male after 10 months on Avodart 0.5mg/day and 5% minoxidil once a day, no surgery. *Case history and photographs courtesy of Dr. Brad Wolf.*

Finasteride also works to reverse prostatic hypertrophy by decreasing gland volume by 25%. With a smaller prostate the ability of a biopsy to find cancer increases. Therefore, physicians are more likely to pick up a high-grade cancer upon biopsy. Dr. Thompson states that a man receiving finasteride was 21% less likely to have high-grade prostatic intraepithelial neoplasia (PIN) on biopsy. The fact is we must treat many patients with finasteride to prevent prostatic cancer in one case. As a hair restoration surgeon, this fact does little to discourage me from prescribing it. While my patients seek this drug for cosmetic reasons, it is most reassuring to think that I may prevent just one of the thousands of men on this drug from developing prostate cancer. There are certainly respectable urologists whose opinions differ sharply from the above. Finasteride does not decrease the androgen that promotes prostate cancer, it increases it. Testosterone, not dihydrotestosterone, is the major androgen that promotes the growth of prostate cancer. Treatment with finasteride increases the level of testosterone within the prostate tenfold.

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Notes from the Editor Emeritus
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Some have disputed that the statistics do not clearly show a 25% reduction in prostate cancer prevalence. Keep in mind that the above studies were done with finasteride 5mg and not the 1mg dosage used in male pattern hair loss. Perhaps these arguments are best left to statisticians.

Testosterone

Testosterone supplementation is common among middle-age men and younger body builders. These men often seek our advice and many are candidates for finasteride. If finasteride does raise interprostatic levels of testosterone significantly, should we be concerned over long-term cancer risks in men receiving both of these drugs simultaneously? Accelerated hair loss has been observed in men receiving exogenous testosterone. Will finasteride combat any additional hair loss caused by exogenous testosterone?

Side Effects

Most of our patients seem more concerned about the sexual side effects of finasteride than the cancer reduction potential. The sexual side effects (decreased libido) in the original studies were found to occur in approximately 2% of patients. The exact percentage of sexual side effects in my patients is extremely difficult to gauge. Is it more than 2% or less? Is it age related? Do older men have a greater chance of experiencing decreased libido from 5 alpha-reductase therapy? This is a complex issue and one in which the power of suggestion certainly plays a role. We are called to a prospective analysis of the quality of life data from the Prostate Cancer Prevention Trial. In this, Moinpour found that the drug had no clinically significant effects on sexual function. I am not suggesting in this editorial that he is correct, but rather that there are various opinions on a subject difficult to study.

Testicular Pain

Patients have reported developing unilateral testicular pain after starting finasteride 1mg. The pain resolves with discontinuation of the drug. There are reports of recurrence after a rechallenge, implicating a drug etiology. This rare side effect should be noted by hair restoration surgeons, as the aftermarket prevalence may be higher than the reported incidence by Merck.

Gynecomastia and Breast Cancer

It appears that gynecomastia can be related to finasteride at a dosage of 5mg. Green et al. concluded that "because gynecomastia is due to an increased ratio of estrogen to androgen, it is biologically plausible that finasteride causes gynecomastia." For Propecia®, the incidence has been reported to be approximately 0.4% and slightly higher for older men receiving 5mg daily. Gynecomastia can be painful and is often reversible upon stopping. Gynecomastia and drugs responsible for its causation have been associated with breast cancer in men. Whether finasteride therapy can induce breast cancer in men is not known (Figure 3).

Figure 3. Patient with possible drug-related gynecomastia. *Photograph courtesy of Dr. Eric Eisenberg.*

Seborrheic Dermatitis

There are reports of finasteride improving seborrheic dermatitis. Those limited case histories are anecdotal and must be taken in their proper context. However, there are hair restoration surgeons who have reported patients stating a definite improvement of their seborrheic dermatitis while on this drug. Others have seen no such correlation.

Behavioral Interactions

The subject of finasteride and depression is also a concern. To the best of my knowledge, there was no statistical increase in the incidence of depression in patients taking finasteride in the original trials. An article in 2006 by Rahimi-Ardabile et al., titled "Finasteride-induced depression: A prospective study," was published in *BMC Clinical Pharmacology*. This was a prospective study that did not include a control group. Their findings "suggest" that finasteride might induce depressive symptoms. The data suggested only a slight change and very few conclusions can be drawn from this paper. The authors point out that steroid hormones, including androgens, undergo extensive metabolism in the brain. Several enzymes, such as 5 alpha-reductase, intervene in brain androgen and steroid metabolism. Some studies have shown that serum DHT level (and its equilibrium within the brain) is inversely associated with depression. Furthermore, 5 alpha-reductase inhibitors are compounds that inhibit production of allopregnanolone. This compound is decreased in men with unipolar major depressive disorders. It is still a "stretch" to clinically prove that finasteride does indeed induce depression. There are no reports suggesting motor neuron effects with long term use of finasteride, or other 5 alpha-reductase inhibitors. The jury is still out on this one and we remain vigilant for additional information.

Questions have also been raised concerning the safety of 5 alpha-reductase inhibitors in managing long-term risk for neurodegenerative diseases such as Alzheimer's. Once again, allopregnanolone is reduced by treatment with 5 alpha-reductase inhibitors. This compound may be very important to human health and behavior. Decreasing allopregnanolone could, theoretically, lead to problems in patients diagnosed or prone to Alzheimer's.

World Anti-Doping Agency

Finasteride is not, in itself, a performance-enhancing substance. It is known to be a "masking agent" for a number of performance-enhancing steroids, and therefore banned by the World Anti-Doping Agency (WADA). Tests demonstrated that the use of finasteride may cause serious problems when interpreting steroid profiles and screening tests in athletes. Furthermore, the WADA code organization developed a metabolite test for detection of a single oral dose of finasteride for up to 90 hours. Hair restoration surgeons with patients participating in high school, college, or professional athletics, and who are currently taking any 5 alpha-reductase inhibitor, finasteride, or dutasteride, should be aware of this ban.

Spermatogenesis

An article by Liu et al., "Propecia®-induced spermatogenic failure: a report of two cases," (published online December 5, 2007, and currently at press in *Fertility and Sterility*) reported two cases of infertile patients with azoospermia or severe oligospermia, both of whom showed significant improvement in sperm concentration six months after the discontinuation of finasteride. What do we make of two cases? If one of my patients is having difficulty with conception, I advise him to see a reproductive specialist and be sure to inform the physician that he is on finasteride. Certainly, those with oligospermia should consider discontinuation of the drug until conception. It is difficult to even comment, much less give advice, on such isolated cases as the true meaning of this has yet to be discovered.

Conclusion

5 alpha-reductase inhibitors have proven to be important pharmaceutical agents to all hair restoration surgeons. We cannot expect the pharmaceutical companies to provide us with all the answers to all the questions in the above discussion. The entire field of hair restoration surgery will continue its ongoing vigilance and dissemination of information regarding these important drugs. No real conclusive evidence has emerged to implicate these agents as causing additional behavioral, endocrine, or carcinogen related side effects.

Dr. Richard Shiell, the ever vigilant mentor of our Society, stated it best when concerning the hair transplant surgeon's responsibility for drug surveillance of our patients:

"Hair transplant surgeons are in a unique situation to gather some worthwhile statistics on this subject as 1) our patients are mostly adult males; 2) our patients tend to stay with us for many decades from 25 years of age; 3) the patients are incredibly "faithful" and the percentage who wander to other surgeons is not high; and 4) because of this close relationship I think that there would be a very high probability that we would hear from the patient if a breast or prostate abnormality occurred as most have heard about the report linking finasteride with prostate cancer. (I have had 3 breast lumps reported but no gynecomastia or prostate problems over the past decade.) This is amazing as many of my patients are well over 70 and have been with me for more than 35 years."

—Richard Shiell; quote taken from personal correspondence, February 16, 2008.

Suggested Reading

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The ISHRS Achieves ACCME Reaccreditation with Commendation!

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Murray Kopelow, MD, MS, FRCPC

Date of Decision March 30, 2008
Expiration of Term March 2014

Two years ago the ISHRS went through the initial accreditation process of the Accreditation Council for Continuing Medical Education (ACCME) and proudly received the most an initial applicant could receive—2-year provisional accreditation. No sooner than when we received the notification of receiving initial accreditation did we begin the 18-month long process for full reaccreditation.

The process included writing and assembling a detailed and lengthy report of 500 pages with 15 sections including topics such as CME mission statement, planning process, business management and policies, organizational framework, standards for commercial support, and program evaluation. For each section we had to prove in multiple ways how we were compliant.

The process also included assembling a file folder for each educational activity that we offered in the past 3 years that included pertinent documentation specifically requested by the ACCME to again prove our compliance with the many policies.

Finally, the process included an in-person interview and site survey. This past October, Drs. Paul Cotterill and Bob Haber, together with Ms. Victoria Ceh (Executive Director) and Kimberly Miller (HQ and Administrative Manager), participated in the site survey with two ACCME surveyors at the ISHRS headquarters office. Files were examined and all questions regarding educational activities as they relate to ACCME policies were fair game.

Being the overachievers that we are, over the years we have gone above and beyond the standard acceptable mechanisms and strived to put in place the best processes available within our means because, ultimately, we knew this would produce the highest level education for our members and for the field of hair restoration surgery.

We are extremely proud to report that the hard work of many volunteers, committees, and staff who have worked toward this effort has paid off. The ISHRS recently received the decision from the ACCME on the arduous reaccreditation process. We have received "accreditation with commendation"! The notation of "with commendation" is the highest level a provider can receive and means we are accredited for 6 years, as opposed to the standard 4 years that most providers receive. This is a very special distinction.

We all should be very proud of our Society and of what we have achieved. As an educational society we now stand out amongst our peers as being leaders in education.

Kimberly Miller, Bob Haber, Paul Cotterill, and Victoria Ceh, in the ISHRS headquarters office, Geneva, IL, for the ACCME site survey, October 22, 2007.

2. All these forms of hair loss, at least in principle, are of a reversible nature. While this is widely recognized for alopecia areata and telogen effluvium, it is important that we also understand androgenetic alopecia as a—fundamentally—reversible condition. How else could one ever explain, for example, minoxidil-, finasteride-, cyclosporine A-, or ACTH overproduction-induced regrowth of hair in a balding scalp skin territory (more precisely: the re-transformation of vellus into terminal hair follicles by these agents)?
3. There is still no firm evidence that, even in very long-standing cases of androgenetic alopecia, the total number of hair follicles present per area of scalp skin declines more than marginally, if at all. Instead, these balding skin regions show massive, cosmetically undesired transformation of terminal into tiny vellus hair follicles. Essentially the same holds true for alopecia areata, where permanent hair follicle loss occurs as an extreme exception, if ever. To put it bluntly: In the vast majority of patients with even massive hair loss, there is essentially no loss of hair follicles! Thus, even when a follicle has become miniaturized beyond recognition by the naked eye, it still has the potential of retransformation and of generating large hair shafts.
4. There is no firm evidence whatsoever that there is anything basically wrong with the epithelial stem cells of vellus hair follicles in balding scalp skin regions, compared to those of non-balding or immediately adjacent terminal hair follicles. Recent meeting reports from the outstanding hair follicle stem cell laboratory of George Cotsarelis, in fact, suggest that vellus hair follicles have pretty much the same complement of epithelial hair follicle stem cells in the bulge region of their outer root sheath as large terminal ones. No one aware of points 2 and 3 will be surprised about this—how else could any vellus follicles ever make it back into the shiny world of terminal hair follicles if it had lost the epithelial stem cells that are an essential prerequisite for such an astounding miniorgan-transformation, and how else could they continue to engage in normal cycling patterns?
5. In stark contrast, patients with cicatricial (scarring) alopecia do have a major epithelial stem cell problem, and it is no surprise that this form of alopecia is notoriously irreversible. Here, both vellus and terminal hair follicles progressively lose their capacity to regenerate because their epithelial stem cells eventually suffer damage that is beyond repair. Alas, cicatricial alopecia represents a very small minority of all hair loss patients seen in clinical practice and, therefore, does not concern us in the current context.

Considering Stem Cell–Based Therapy

The simple facts above allow only one conclusion: The most common forms of hair loss (see 1) are not a stem cell problem, and have nothing wrong with the number of hair follicles available for hair shaft production. Therefore, one really wonders where the basic stem cell defect lies that supposedly "requires" correction by stem cell–based therapies. Why, then, should stem cells here be beneficial at all?

Two basic arguments are sometimes invoked to defend stem cell–based therapy of common hair loss disorders:

1. On the one hand, relatively crude mixtures of fairly undifferentiated epithelial cells that contain at least some stem cells, brought together with inductive fibroblasts, suffice for primitive hair follicles to self-assemble from appropriately self-sorted and aggregated cell populations in mammalian skin. Thus, hair follicle neogenesis appears deceptively simple (even though we are far from fully understanding the underlying molecular controls). On the other hand, it has proven rather difficult to reconvert vellus into terminal follicles in clinical practice (indeed, past pharmaceutical research has failed in generating highly efficient and reliable, long-lasting vellus-to-terminal converting drugs for safe clinical use, so that we are still stuck with two "children of serendipity"—finasteride and minoxidil—whose overall performance remains disappointing). Therefore, so this argument goes, let's just not fool around any longer with the hard and disappointing labor of trying to induce a vellus-to-terminal conversion. Instead, let us simply exploit stem cells to induce entirely new hair follicles! (And, who knows, maybe this will even stimulate neighboring vellus follicles to grow larger again?)
2. Maybe, if one somehow manages to increase the number of stem cells in the vellus follicles of balding scalp skin by some form of intracutaneous injection, the follicles will get bigger again and eventually can thus be reverted to their old, terminal splendor.

Argument 2 remains a theoretical possibility. However, precisely targeted delivery of such stem cell–based therapy to just the right area of tiny, unpigmented, and therefore hardly visible vellus follicles, surely must be fiendishly difficult (not to mention the associated regulatory nightmares for such cell-based therapy!). Also, if the epithelial stem cell compartment in a vellus follicle is fairly normal, anyway, and if Nature can so easily convert vellus into terminal follicles without evidence that it, first, has to engineer prior changes in the bulge, why do we need such therapy at all?

Much more likely, vellus-to-terminal hair follicle conversion would greatly be facilitated if we managed to identify agents that recruit more inductive fibroblasts from the hair follicle's connective tissue sheath into its dermal papilla (whose volume is thought to directly correlate with the volume of the hair matrix and, thus, with hair follicle size and hair shaft diameter). While it is conceivable that the injection of mesenchymal hair follicle stem cells might be beneficial for follicular dermal papilla enlargement, again, it is far from clear whether they (rather than ordinary, inductive connective tissue sheath fibroblasts) are really needed—not to mention the formidable technical difficulties of precisely targeted cell injection.

If you like argument 1 instead, you would probably also advocate buying a new house next door, rather than fixing the old one's broken front door, right…? Doesn't strategy 1 smack of "therapeutic overkill" to you? And are you not in-

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viting potential trouble that was definitely uncalled for (such as the theoretical risk of malignant degeneration of injected epithelial stem cells that have escaped normal controls and that, for example, give rise to basal cell carcinoma; or the production of ugly cysts or painful, chronically inflamed foreign body granulomata, instead of functional hair shafts)?

If all that doesn't worry you the least bit, what about the cosmetic results that you can expect? Remember: The beauty of terminal hair, to a large extent, lies in its luster, color, and durability, and in the symmetry and geometry of its arrangement, especially in the perfection of the alignment of hair shafts towards each other. Therefore, just forcing out of a balding plate a few miserable, malaligned hair shafts that, to top it off, more resemble scrotal hair than that of the beautiful forelock fancied by your client/patient, cosmetically, is unlikely to be a winning ticket…

Multiple investigators have, by now, impressively demonstrated in several elegant rodent models that hair follicle neogenesis is indeed possible, even in adult and aging mammalian skin. Therefore, I do not have any doubts that the iatrogenic induction of new terminal hair follicles in the balding and aging human scalp is possible, in principle. Yet, I still wait for at least theoretically convincing strategies to be put forward by the exponents of this "overkill" approach to alopecia management on how they will achieve (and, actually, guarantee) cosmetically acceptable hair beauty (i.e., perfect hair shaft alignment, geometry, cuticle structure, and arrangement) after successful folliculoneogenesis.

You see: Acidic drops of doubt are dripping into the optimistically sparkling "hair regeneration" claret that we are being toasted with so frequently these days, and we are left with the simple, initial question: Do we need follicle neogenesis for the management of common forms of alopecia at all?

Except for the exceptionally few patients with a completely "burned-out" form of cicatricial alopecia, or a congenital hair aplasia, I just fail to recognize why hair follicle stem cells (epithelial, mesenchymal) should be required, or might at least offer significant therapeutic benefit at acceptable cost and risk, in any of the common alopecias. The same goes for iatrogenic hair follicle neogenesis—a true wonder of applied developmental biology, but not a major new "cure" for hair loss disorders. Hair follicle–associated stem cells undoubtedly hold a lot in store for regenerative medicine—well beyond skin and the hair follicle—but they are not going to put hair transplant surgeons predictably out of business any time soon.

Of course, I have been wrong before, and may be wrong again…. And yet, in my view, if we ever wish to live up to the ancient, unmet therapeutic challenges posed to us by androgenetic alopecia, common causes of effluvium, and alopecia areata, we must labor on quite different frontiers: What is really needed is concerted and systematic research geared at developing efficient, predictable, and long-lasting

a. hair cycle control therapy,
b. stem cell protection therapy,
c. immune privilege restoration therapy,
d. exogen inhibition, and
e. vellus-to-terminal conversion by directing hair follicle fibroblast trafficking from the connective tissue sheath into the follicular dermal papilla.

But those are other stories, to be told in later issues of this *Forum*.

For now, suffice it to summarize: Classical hair restoration surgery has a future, and so does hair follicle stem cell therapy. But I predict that the latter's future does not lie in the management of common alopecias.✧

Editor's note: Ralf Paus received his medical degree from the Berlin Free University and served as a Postdoctoral Research Fellow in the Department of Dermatology at Yale University. He is currently Professor of Dermatology and Head of Experimental Dermatology at the University of Lübeck, Germany. Dr. Paus has authored over 250 peer-reviewed publications and is a world-renowned researcher in the fields of hair biology, regenerative medicine and neurobiology, neural endocrinology, and neuroimmunology of the skin. Dr. Paus is editor of the journal *Experimental Dermatology* and Section Editor of the *Journal of Investigative Dermatology*.